PATENT
Attorney Docket No. **STRATA-06663**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Conrad et al.	
Serial No.:	10/087,641	Group No.: 1651
Filed:	03/01/02	Examiner: Davis
Entitled:	**Improved Skin Substitutes And Uses Thereof**	

DECLARATION OF DR. B. LYNN ALLEN-HOFFMANN

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Commissioner for Patents
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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: May 7, 2004 By: Mary Ellen Waite

I, Dr. B. Lynn Allen-Hoffmann, state as follows:

1. My present position is President and CSO of Stratatech Corporation. I am also a Professor at the University of Wisconsin-Madison.

2. I have reviewed the Final Office Action dated January 13, 2004 and the references cited therein, U.S. Pat. No. 5,989,837 and Yang et al., Artificial Organs 24(1):7-17 (2000).

3. I am an inventor of the '837 patent which was cited as prior art. It is my understanding that the Examiner has asserted that the '837 patent teaches culturing a dermal equivalent onto which keratinocytes have been seeded at an interface until the keratinocytes stratify. As support for this assertion, which is incorrect, the Examiner cites to Column 15, lines 20-39 of my previous patent. The pertinent text is as follows:

Organotypic cultures of BC-1-Ep/SL cells exhibit normal squamous differentiation

To confirm that the BC-1-Ep/SL keratinocytes can undergo normal squamous differentiation, the cells were cultivated in organotypic culture. Differentiation of keratinocytes cultured on a plastic substrata under medium promotes growth and limited differentiation. Specifically, human keratinocytes become confluent, stratify and produce a multilayered sheet that is similar to stratified epithelium. However, by light and electron microscopy there are striking differences between the architecture of the multilayered sheets formed in tissue culture and intact human skin. Organotypic culture is a technique to culture keratinocytes under in vivo-like conditions. Specifically, the cells adhere to a physiological substrata, fibrillar collagen embedded with dermal fibroblasts, and are lifted to the air-medium interface so that the cells can grow with their upper sheets air-exposed and with the proliferating basal cells closest to the gradient of nutrients provided by diffusion through the collagen gel. Under these conditions, correct tissue architecture is formed.

4. The Examiner has taken this general description of organotypic culture out of context. This passage states that keratinocytes adhere to a physiological substrata (the dermal equivalent of the present invention), which is then lifted to the air-medium interface so that stratification can occur. This passage does not state the conditions under which the adhering step is conducted. To put this passage in the proper context, one must look elsewhere in the '837 patent for a more complete description of the organotypic culture process. This information can be found in the '837 patent, for example, at column 9, lines 27-51:

Formation of Organotypic Cultures

Organotypic cultures were grown as previously described (N. Parenteau, 1994). A collagen raft was formed by mixing normal human neonatal fibroblasts, CI-1-F, with Type I collagen in 10% FCS+F12+penicillin/streptomycin. Rafts were allowed to contract for 5 days. The parent cells, BC-1-Ep (5^{o}) and the BC-1-Ep/SL (38^{o}) cells were plated on the rafts at 3.5 X 10^{5} cells in 50 µl 0.2% FCS+3F12:1DME+HC+Ade+Ins+CT+P/S containing 1.88 mM calcium. Cells were allowed to attach 2 hours before adding an additional 13 mls of media (Day 0). On Day 1 and 2 cells were refed. On Day 4, cells were lifted to the air interface with cotton pads and switched to cornification medium (2% FCS+3F12:1DME+HC+Ade+Ins+CT+P/S containing 1.88 mM calcium). Cells were fed

cornification medium every three days. On Day 15 rafts were fixed with freshly made modified Karnovsky's fixative consisting of 3% glutaraldehyde and 1% paraformaldehyde in 0.1 M cacodylate buffer, pH 7.4, at room temperature for 3 hours. Before removing the culture media, fixative was gently added to the cells on top of the raft to prevent cornified layers from floating away. Subsequently, the culture media was aspirated and the culture wells filled with fixative. The raft was cut in half with one half processed for light microscopy and the other half for electron microscopy.

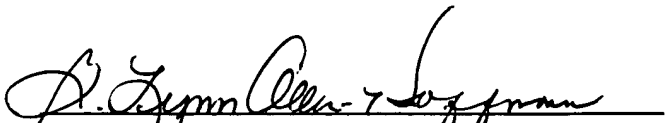
5. This passage describes the following steps regarding seeding the dermal equivalent:

Cells were allowed to attach 2 hours before adding an additional 13 mls of media (Day 0). On Day 1 and 2 cells were refed. **On Day 4, cells were lifted** to the air interface with cotton pads and switched to cornification medium (2% FCS+3F12:1DME+ HC+Ade+Ins+CT+P/S containing 1.88 mM calcium).

As can seen, following seeding, the seeded dermal equivalent was submerged for four days prior to lifting. In light of this teaching, it is apparent that the Examiner has taken the teachings of passage at Column 15, lines 20-39 out of context in suggesting that this passage supports "culturing the keratinocytes at the air interface until the keratinocytes stratify." The '837 patent teaches that the seeded dermal equivalent is submerged for a period of time prior to lifting. Thus, the seeded dermal equivalent is not maintained at the air interface following seeding.

6. I further declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: May 6, 2004



Dr. B. Lynn Allen-Hoffmann